Biomarkers for risk stratification of patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention: Insights from the Platelet Inhibition and Patient Outcomes trial

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Background The incremental prognostic value of admission measurements of biomarkers beyond clinical characteristics and extent of coronary artery disease (CAD) in patients treated with primary percutaneous coronary intervention (PPCI) for ST-elevation myocardial infarction (STEMI) is unclear.

Methods Centrally analyzed plasma for biomarker measurements was available in 5,385 of the STEMI patients treated with PPCI in the PLATO trial. Extent of CAD was graded by operators in association with PPCI. We evaluated the prognostic value of high-sensitivity cardiac troponin T, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and growth differentiation factor 15 (GDF-15) beyond clinical characteristics and extent of CAD using Cox proportional hazards analyses, C-index, and net reclassification improvement (NRI). Outcomes were cardiovascular death (CVD) and spontaneous myocardial infarction (MI).

Results Angiographic data on extent of CAD improved the prediction of CVD compared to clinical risk factors alone, increasing the C-index from 0.760 to 0.778, total NRI of 0.31. Biomarker information provided additional prognostic value for CVD beyond clinical risk factors and extent of CAD, C-indices ranging from 0.792 to 0.795 for all biomarkers, but with a higher NRI for NT-proBNP. Extent of CAD and high-sensitivity cardiac troponin T were not associated with spontaneous MI. The prediction of spontaneous MI beyond clinical characteristics and extent of CAD (C-index 0.647) was improved by both NT-proBNP (C-index 0.663, NRI 0.22) and GDF-15 (C-index 0.652, NRI 0.05).

Conclusions Biomarker measurement on admission is feasible and provides incremental risk stratification in patients with STEMI treated with PPCI, with NT-proBNP and GDF-15 being most valuable due to the association with both CVD and spontaneous MI. (Am Heart J 2015;169:879-889.e7.)

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Outcomes in patients with ST-elevation myocardial infarction (STEMI) have been substantially improved by early reperfusion with primary percutaneous coronary intervention (PPCI).[1] However, recurrent events after the acute phase of STEMI are common, indicating the need for additional strategies to continue to improve the outcome of these patients.[2,3] Identification of high-risk patients is essential for the initiation of appropriate therapy to reduce the risk of events.[1,4,5] Conventional risk scores rely on clinical characteristics and physiological parameters to assess the risk of mortality.[4-7] Angiographic data on the extent of coronary artery disease (CAD) may provide additional prognostic information.[8,9] Furthermore, markers of myocardial dysfunction (N-terminal pro–B-type natriuretic peptide

[NT-proBNP]), myocardial necrosis (high-sensitivity cardiac troponin T [cTnT-hs]), and oxidative stress (growth differentiation factor 15 [GDF-15]) have been shown to improve the risk prediction over traditional risk factors.[10-12] However, the individual and combined values of these biomarkers over traditional risk factors and the extent of CAD in patients with STEMI treated with PPCI remain unclear.

This PLATO biomarker substudy evaluated the incremental value of admission measurements of 3 biomarkers (cTnT-hs, NT-proBNP, and GDF-15) and the angiographic extent of CAD to clinical characteristics for the risk stratification of patients with STEMI treated with PPCI.

Methods

Design

The present analysis is a report from the biomarker substudy of the prospective PLATO trial (http://www.ClinicalTrials.gov no. NCT00391872). Details of the design and results have been published.[13,14] Inclusion criteria for the present investigation were as follows: (1) presentation with STEMI (typical symptoms plus persistent ST-elevation of ≥1 mV for ≥20 minutes not known to be preexisting or resulting from a coexisting disorder in ≥2 contiguous leads or new or presumed new left bundle-branch block), (2) invasive treatment using PPCI; and (3) availability of biomarker measurements from samples obtained at time of randomization and full covariate information. The study protocol was approved by an independent ethics committee or institutional review board, and informed consent was required before any study procedure. The PLATO study complied with the Declaration of Helsinki.

Objective

The present analysis sought to evaluate the prognostic value of the extent of CAD and admission measurements of 3 biomarkers (cTnT-hs, NT-proBNP, and GDF-15) for the risk stratification of patients with STEMI treated with PPCI. Angiographic extent of CAD was graded in association with PPCI according to 3 categories: nonsignificant or 1-vessel disease, 2-vessel disease, and 3-vessel or left main disease. *Significant CAD* was defined as a visual coronary stenosis >50%.

Events

The main outcome measures were cardiovascular death (CVD) and spontaneous myocardial infarction (MI). Myocardial infarction was defined in accordance with the universal definition proposed in 2007.[15] *Spontaneous MI* was defined as any MI except MI related to percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (type 4a and type 5 MI). The reason for this approach was the greater clinical relevance of spontaneous MI as compared to procedure-related MI.[16] Before the analyses, it was decided to exclude stroke as an end point due to small number of events and different etiology and risk associations. An independent blinded central adjudication committee adjudicated all end points.

Laboratory analyses

Venous blood samples were obtained at the time of randomization, a median of 42 minutes (interquartile range [IQR] 83 minutes) after admission. After centrifugation, plasma samples were frozen in aliquots and stored at −70°C until blinded analysis at the Uppsala Clinical Research Center laboratory. High-sensitivity cardiac troponin T (lot number 153 401), NT-proBNP, and GDF-15 were determined with sandwich immunoassays on the Cobas Analytics e601 and C501 Immunoanalyzer (Roche Diagnostics, Penzberg, Germany) according to the instructions of the manufacturer. The manufacturer-provided analytical range of cTnT-hs is 3 to 10,000 ng/L, and the limit of detection is 5 ng/L. The coefficient of variation is <10% at 14 ng/L, the 99th percentile upper reference limit (URL) for healthy subjects.[17] For NT-proBNP, the analytical range extends from 5 to 35,000 ng/L. The lower limit of detection is 5 ng/L, and the lowest concentration with a coefficient of variation <20% is 50 ng/L. The URL is defined at 300 ng/L for men and 400 ng/L for women, corresponding to the URL in an apparently healthy elderly population.[18] The Elecsys GDF-15 precommercial assay is reported by the manufacturer to have a lower detection limit of <10 ng/mL, with an interassay coefficient of variation of 2.3% at 100 ng/mL and 1.8% at 17,200 ng/mL. The intra-assay coefficient of variation is 0.8% at 1,100 ng/mL and 0.9% at 18,600 ng/mL. The URL is defined as 1,200 ng/L, corresponding to the URL in an apparently healthy elderly population.[19] The Uppsala Clinical Research Laboratory performed twice-daily quality checks on control samples to ensure correct calibration of biomarker assays according to the ISO 15189 accreditation.

Statistical analyses

Analyses were performed using the PLATO safety population, comprising patients who had received at least 1 dose of the study drug. Characteristics were summarized using frequencies and percentages for categorical variables and median and 25th and 75th percentiles for continuous variables. Trends in categorical variables were evaluated using the Cochran-Armitage trend test. The relationships between biomarkers and extent of CAD were analyzed using Spearman's rank order correlation, and the relationships between the biomarkers were analyzed using Pearson product moment correlation.

Outcomes in relation to biomarkers and extent of CAD were analyzed using Cox proportional hazards models. The following variables were considered for the baseline risk model: age, gender, diabetes mellitus, hypertension,

smoking, Killip class, admission heart rate, admission systolic blood pressure, history of congestive heart failure, peripheral arterial disease, cystatin C (log transformed), previous MI, previous PCI, previous CABG, and randomized treatment arm (ticagrelor/clopidogrel). Strong correlation of hypertension, smoking status, and previous PCI with other predictors led to the removal of these factors from the baseline model. The outcomes in relation to randomized treatment and biomarker were analyzed using a model including treatment group, biomarker quartile group, and treatment by biomarker interaction as covariates.

The assumption of proportional hazards was assessed visually using log-cumulative hazard plots and by extending the Cox model with a time by biomarker/CAD interaction factor. Proportional hazards were assumed. The cumulative sums of Martingale-based residuals indicated that a log transformation was needed for cTnT-hs, NT-proBNP, GDF-15, and cystatin C. High-sensitivity cardiac troponin T, NT-proBNP, and GDF-15 were evaluated as natural log-transformed continuous variables and as quartiles. Likelihood ratio tests were performed to evaluate whether the global model fit improved after the addition of extent of CAD or a biomarker. The overall C-index was used to quantify the discriminatory ability of the multivariable models.[20] The C-index is a measure for the goodness of fit of a regression model, a value of 0.5 indicating that a model is no better than chance at making a correct prediction of events and a measure of 1.0 indicating that the occurrence of events is predicted perfectly in the study population.

Continuous (category free) net reclassification improvement (NRI) was calculated to quantify the degree of correct reclassification as a result of adding extent of CAD and biomarkers to the baseline risk model.[21] Net reclassification improvement for events constitutes the net percentage of persons with the event correctly assigned a higher predicted risk. Net reclassification improvement for nonevents constitutes the net percentage of persons without the event of interest correctly assigned a lower predicted risk. Total NRI is the sum of the net percentages of persons with and without the events of interest correctly assigned a different predicted risk.[22] Kaplan-Meier estimates of the cumulative hazard rate were calculated and plotted.

All statistical tests were 2 tailed and performed at the 0.05 significance level. There were no adjustments for multiple comparisons. The Clinical Research section at the Uppsala Clinical Research center conducted the statistical analyses, using SAS software version 9.3 (SAS Institute, Inc, Cary, NC).

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The authors are solely responsible for the design and conduct of this study, all analyses, the drafting and editing of the manuscript, and its final contents.

Results

In the PLATO population, the safety population consisted of the 7,471 STEMI patients who received at least 1 dose of the study drug. Of these patients, 6,144 underwent PCI during index hospitalization. After excluding patients with missing biomarker measurements (n = 711) or other covariate information (n = 48), a total of 5,385 patients were included in the present analysis. Randomized treatment was given for a median of 282 days (IQR 180 days). One patient in the clopidogrel arm and no patients in the ticagrelor arm were lost to follow-up.

Baseline characteristics and event rates for the included compared to excluded STEMI patients are shown in online Appendix Supplementary Tables I and II. Generally, there were no major differences between included and excluded patients, although the excluded group showed slightly higher comorbidity, longer delay until randomization and treatment, and marginally higher event rates.

Extent of CAD correlated weakly with NT-proBNP (Spearman correlation coefficient of 0.13 [95% CI 0.10-0.16, $P < .001$]) and GDF-15 (0.12 [95% CI 0.09-0.14, $P < .001$]) but not with cTnT-hs (online Appendix Supplementary Table III). In addition, all biomarkers correlated: cTnT-hs and NT-proBNP with a coefficient of 0.58 (95% CI 0.57-0.60, $P < .001$), cTnT-hs and GDF-15 with a coefficient of 0.16 (95% CI 0.14-0.19, $P < .001$), and NT-proBNP and GDF-15 with a coefficient of 0.34 (95% CI 0.32-0.36, $P < .001$).

Events

The univariable associations of extent of CAD and biomarkers with outcome are shown in Table I and Figures 1 and 2. Categories of CAD and quartiles of cTnT-hs showed an increasing separation for rates of CVD during follow-up. A more gradual increase in rates of spontaneous MI was observed for extent of CAD but not for cTnT-hs. The highest quartiles of NT-proBNP and GDF-15 showed an early peak and marked separation from lower quartiles in CVD, with a more gradual increase in event rates for each quartile with regard to spontaneous MI. No interactions were observed between quartiles of biomarkers and treatment effect of ticagrelor versus clopidogrel (online Appendix Supplementary Table IV). The distribution of outcomes rates was similar for all biomarkers according to delay between onset of symptoms and randomization (online Appendix Supplementary Figure).

Table I. Occurrence of end points during follow-up according to quartiles of biomarkers and extent of CAD

	CVD			Spontaneous MI		
	No. of events, n (%)	HR (95% CI)	*P*	No. of events, n (%)	HR (95% CI)	*P*
cTnT-hs						
Q1: <41	1344 16 (1.2)			1344, 42 (3.1)		
Q2: 41-147	1349 33 (2.4)	2.07 (1.14-3.77)	<.0001	1349, 41 (3.0)	0.99 (0.64-1.52)	.7231
Q3: 148-583	1347 55 (4.1)	3.49 (2.00-6.09)		1347, 43 (3.2)	1.05 (0.68-1.60)	
Q4: >583	1345 95 (7.1)	6.15 (3.62-10.45)		1345, 49 (3.6)	1.22 (0.81-1.85)	
NT-proBNP						
Q1: <71	1348 16 (1.2)			1348, 18 (1.3)		
Q2: 71-221	1346 24 (1.8)	1.51 (0.80-2.84)	<.0001	1346, 43 (3.2)	2.42 (1.39-4.19)	<.0001
Q3: 222-850	1345 44 (3.3)	2.80 (1.58-4.97)		1345, 54 (4.0)	3.11 (1.82-5.30)	
Q4: >850	1346 115 (8.5)	7.57 (4.49-12.77)		1346, 60 (4.5)	3.59 (2.12-6.08)	
GDF-15						
Q1: <1116	1346 18 (1.3)			1346, 23 (1.7)		
Q2: 1116-1492	1346 26 (1.9)	1.46 (0.80-2.70)	<.0001	1346, 43 (3.2)	1.90 (1.15-3.20)	<.0001
Q3: 1492-2120	1347 37 (2.7)	2.06 (1.19-3.71)		1347, 47 (3.5)	2.07 (1.27-3.46)	
Q4:>2120	1346 118 (8.8)	6.91 (4.33-11.74)		1346, 62 (4.6)	2.90 (1.83-4.78)	
Extent of CAD						
Zero/1-vessel disease	2642 54 (2.0)			2642, 66 (2.5)		
2-vessel disease	1623 63 (3.9)	1.92 (1.33-2.76)	<.0001	1623, 55 (3.4)	1.38 (0.96-1.97)	.0010
3-vessel disease/left main	1120 82 (7.3)	3.66 (2.60-5.16)		1120, 54 (4.8)	2.00 (1.39-2.86)	

Abbreviations: *Q*, Quartile; *HR*, hazard ratio. Hazard ratios represent ratios of each quartile compared to the first.

Prediction models

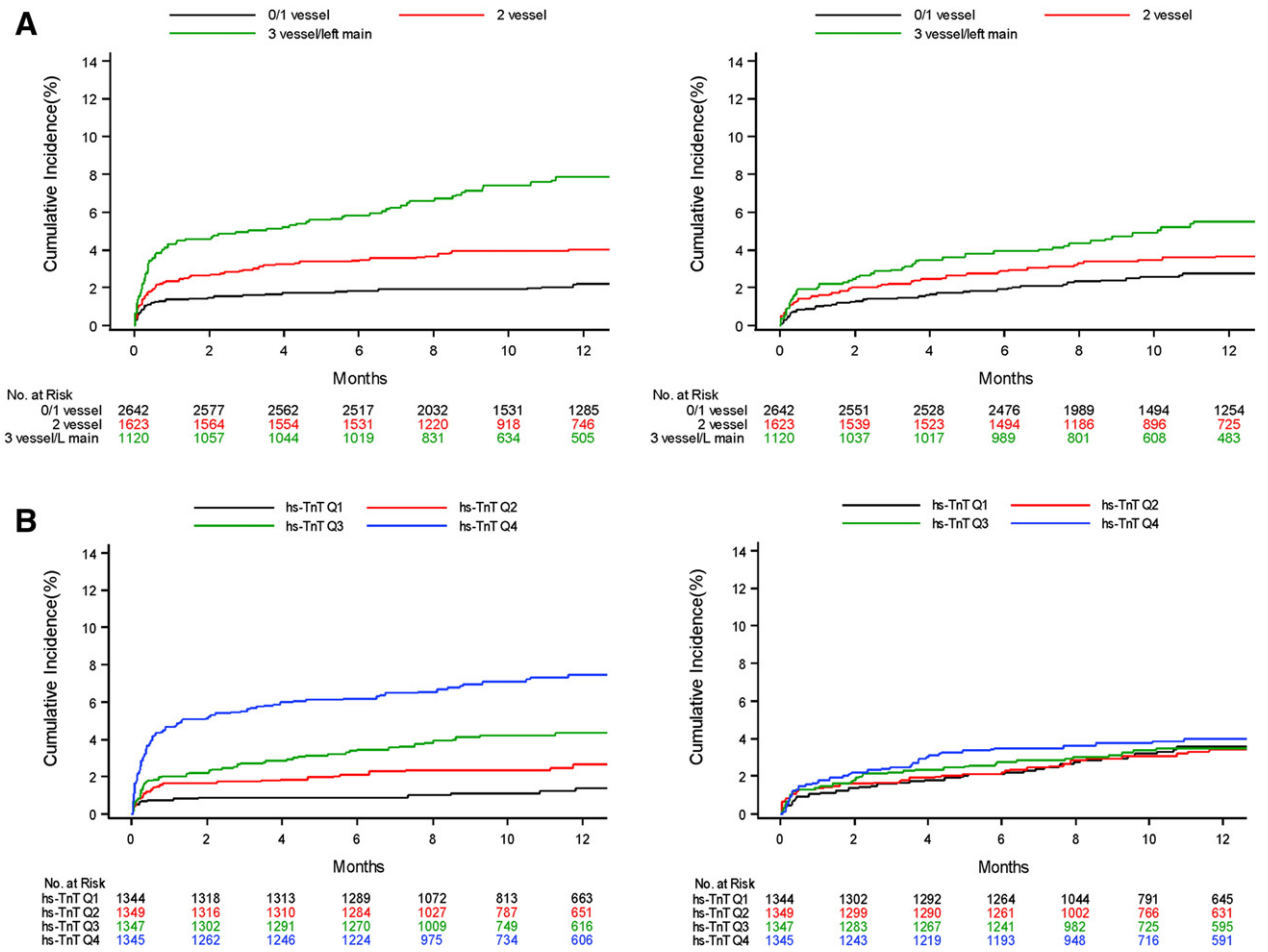
Addition of extent of CAD to a model with clinical risk factors substantially improved the prediction of CVD, increasing the C-index from 0.760 to 0.778, with a total NRI of 0.31 (Table II, Figure 3, online Appendix Supplementary Tables V-VII). Addition of biomarkers further improved the prediction of CVD, regardless of extent of CAD, resulting in similar C-indices between 0.792 and 0.795, but with highest NRI for NT-proBNP. In the subsequent model including NT-proBNP, GDF-15 added more complementary information compared to cTnT-hs as judged by the increase in C-index. Only NT-proBNP and GDF-15 improved the prediction of spontaneous MI, resulting in a pronounced increase in C-index and higher NRI for NT-proBNP, with increase in C-index but only marginally positive NRI for GDF-15 (Table II, Figure 4).

Discussion

The present biomarker substudy in patients with STEMI showed that cTnT-hs, NT-proBNP, and GDF-15 as well as the angiographic extent of CAD improved the prediction of subsequent occurrence of CVD in comparison to clinical information alone. The predictive value of the 3 biomarkers was similar for CVD and independent of the extent of CAD. Only NT-proBNP and GDF-15 showed prognostic value for spontaneous MI during follow-up. Thus, for prognostication of both CVD and spontaneous MI after PPCI in STEMI, NT-proBNP as well as GDF-15 will provide useful information beyond what currently is available from clinical and angiographic data.

Today, most patients with STEMI are referred immediately for PPCI, and risk stratification as a basis for additional treatment starts when information on the extent of CAD is available.[1] The so far recommended and tested risk scores for patients with STEMI such as the TIMI and GRACE score are based only on clinical characteristics.[4-9] Similarly, previous evaluations of the incremental value of biomarkers were mostly limited to single biomarker studies and lacked CAD data.[10-12,23-25] Therefore, the relative prognostic value of these markers over the extent of CAD and each other remains unclear. This study investigated the extent of CAD and admission levels of 2 widely used biomarkers, cTnT-hs and NT-proBNP, and 1 promising, but currently not generally available, biomarker, GDF-15, in addition to clinical information. Although the extent of CAD was confirmed as a predictor of CVD,[8,9] admission biomarkers provided incremental prognostic information. Thus, the extent of CAD and the levels of biomarkers carry different and complementary information as illustrated by the poor correlation between the level of biomarkers and the extent of CAD. Among the established biomarkers, NT-proBNP and cTnT-hs showed similar prognostic value for the prediction of CVD, but only NT-proBNP was associated with spontaneous reinfarction. Previous studies established the predictive value of both markers for CVD after STEMI.[10,11,23-25] However, the present study is, to our knowledge, the first to report an independent association of admission measurements of NT-proBNP with subsequent spontaneous reinfarction in invasively treated STEMI patients. Natriuretic peptides are secreted by myocardial tissue in response to both wall

Figure 1



Occurrence of CVD (left side of figure) and spontaneous MI (right side of figure) according to extent of CAD (**A**) and quartiles of cTnT-hs (**B**).

stress and myocardial ischemia, possibly explaining the association with CVD and recurrent MI.[26]

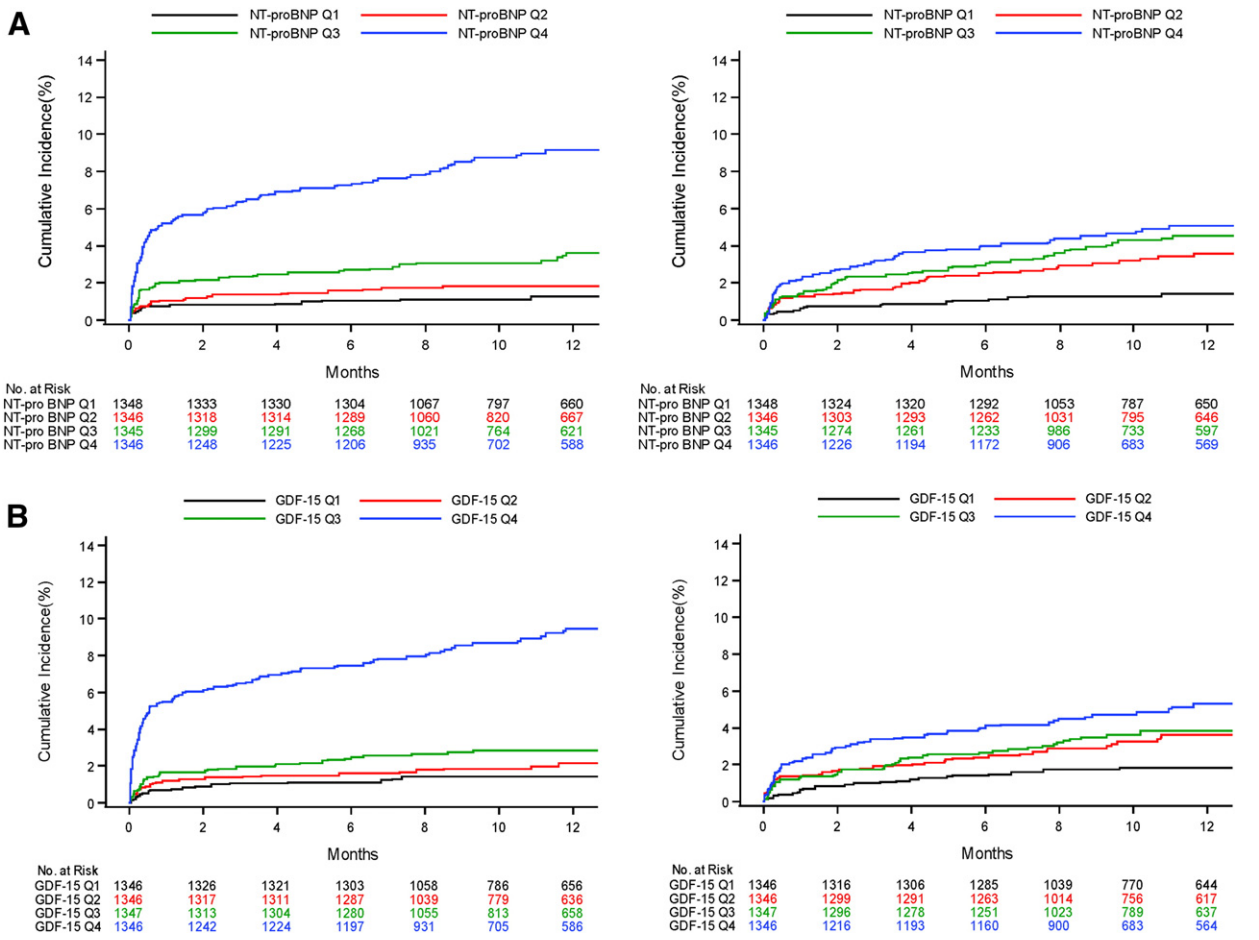
The novel marker GDF-15 showed similar prognostic value for CVD compared to the established markers and was also found to have an association with spontaneous MI, expanding on previous findings in medically treated STEMI patients and patients with non–ST-elevation acute coronary syndrome.[12,27] Growth differentiation factor 15 is a member of the transforming growth factor β superfamily, which is expressed and synthesized rapidly in case of myocardial pressure/volume overload and myocardial ischemia.[28] Moreover, GDF-15 has been associated with atherosclerotic plaque burden in elderly individuals.[29]

The prognostic values of NT-proBNP and GDF-15 beyond the extent of CAD may be explained by their relationship to vulnerability of the myocardium and/or the vessel wall, which might be associated with a larger risk of new plaque ruptures without underlying severe coronary lesions as well as to a larger risk of MI when exposed to ischemia.[30] The preexisting coronary and myocardial vulnerability may also be the reason for a more pronounced elevation of these biomarkers in association with the acute ischemic event.

Clinical implications

Biomarker measurement on admission is an objective tool to aid the physician in the early recognition of high-risk patients potentially benefiting from intensified secondary preventive therapy, for example, early initiation of angiotensin-converting enzyme inhibitors, high-dose statin therapy, and β-blocking agents with intensified follow-up to allow strict evaluation of secondary preventive goals such as blood pressure and lipid values as well as up-titration of angiotensin-converting enzyme inhibitors and β-blocking agents to evidence-based doses,

Figure 2



Occurrence of CVD (left side of figure) and spontaneous MI (right side of figure) according to quartiles of NT-proBNP (**A**) and quartiles of GDF-15 (**B**).

as underdosing of these agents is highly prevalent in patients after MI.[31] Furthermore, biomarkers may be useful to motivate early myocardial imaging or to guide the extent of revascularization, potentially decreasing rates of cardiac death and reinfarction in patients with multivessel CAD.[32]

In this study, there was no interaction between biomarker levels and benefit of ticagrelor, which is in accordance with the experiences of invasively managed non-STEMI patients with elevated cTnT-hs.[33]

Limitations

The generalizability of this study might be limited to patients meeting the inclusion criteria for PLATO. However, the patients included in PLATO seem to represent a broad range of acute coronary syndrome patients fairly well corresponding to the real-life situation. There was a median of 45-minute delay until measurement of biomarkers after admission. Moreover, although the goal of the present study was to evaluate the use of admission measurements of biomarkers, alternative time points of blood sampling might provide complementary information. Furthermore, angiographic data were not analyzed by an independent core laboratory. The relative prognostic value of the biomarkers and other variables might be different in relation to longer follow-up. Finally, additional investigations are required to explore biomarker–guided management strategies.

Conclusions

In patients with STEMI treated with PPCI, measurement of biomarkers on admission is feasible and may be used to identify high-risk patients potentially benefiting from intensified management strategies. The superior prognostic value of NT-proBNP concerning both CVD and spontaneous MI and the limited influence of time delay make NT-proBNP the most suitable currently available

Table II. Benefit of extent of CAD, cTnT-hs, NT-proBNP, and GDF-15 addition to prediction models of end points

	n	C-index	NRI total	NRI among events	NRI among nonevents	*P* value LR test
CVD	5385					
Model 1*		0.760	–	–	–	–
Model 1 + extent of CAD		0.778	0.31397	0.27244	0.04153	<.0001
Model 1 + CTnT-hs		0.782	0.36913	0.17723	0.19189	<.0001
Model 1 + NT-proBNP		0.782	0.51094	0.30417	0.20677	<.0001
Model 1 + GDF-15		0.780	0.28632	0.05387	0.23246	<.0001
Model 2†		0.778	–	–	–	–
Model 2 + CTnT-hs		0.795	0.38575	0.19803	0.18772	<.0001
Model 2 + NT-proBNP		0.792	0.47495	0.28445	0.19049	<.0001
Model 2 + GDF-15		0.795	0.30566	0.06316	0.24250	<.0001
Model 3‡		0.792	–	–	–	–
Model 3 + CTnT-hs		0.797	0.18349	0.06316	0.12032	.0037
Model 3 + GDF-15		0.804	0.18255	0.01770	0.16486	<.0001
Model 4§		0.797	–	–	–	–
Model 4 + GDF-15		0.809	0.14660	0.00879	0.13781	<.0001
Spontaneous MI	5385					
Model 1*		0.638	–	–	–	–
Model 1 + extent of CAD		0.647	0.16046	0.14295	0.01751	.0704
Model 1 + CTnT-hs		0.639	0.03987	0.01224	0.02763	.6312
Model 1 + NT-proBNP		0.658	0.29251	0.17812	0.11440	.0027
Model 1 + GDF-15		0.646	0.06507	–0.10126	0.16633	.0120
Model 2†		0.647	–	–	–	–
Model 2 + CTnT-hs		0.647	0.03348	0.00980	0.02368	.6150
Model 2 + NT-proBNP		0.663	0.21806	0.10599	0.11207	.0042
Model 2 + GDF-15		0.652	0.04869	–0.11519	0.16388	.0133
Model 3‡		0.663	–	–	–	–
Model 3 + CTnT-hs		0.667	0.14006	0.08020	0.05985	.1530
Model 3 + GDF-15		0.668	0.05656	–0.07530	0.13185	.0351
Model 4§		0.667	–	–	–	–
Model 4 + GDF-15		0.671	0.05399	–0.07480	0.12879	.0360

Abbreviation: *LR*, Likelihood ratio test of nested Cox proportional hazards models.
* Model l: age, gender, diabetes mellitus, Killip class, admission heart rate, admission systolic blood pressure, history of congestive heart failure, peripheral arterial disease, cystatin C (log transformed), previous MI, previous PCI, previous CABG, and randomized treatment arm (ticagrelor/clopidogrel).
† Model 2: model 1 + extent of CAD.
‡ Model 3: model 2 + NT-proBNP (log transformed).
§ Model 4: model 3 + cTnT-hs (log transformed).

marker for this purpose. The new biomarker GDF-15 adds incremental information and might be an additional useful tool when more generally available.

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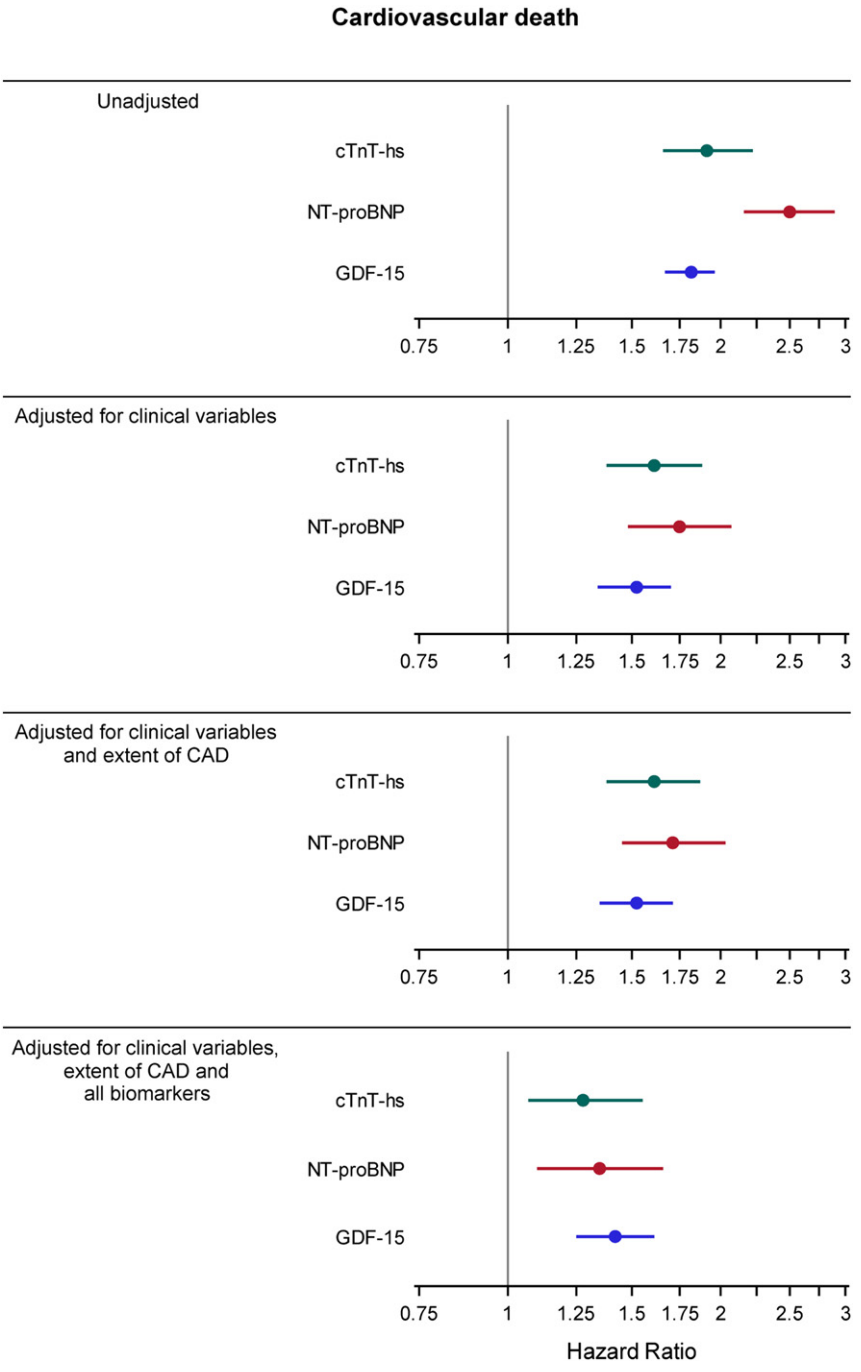
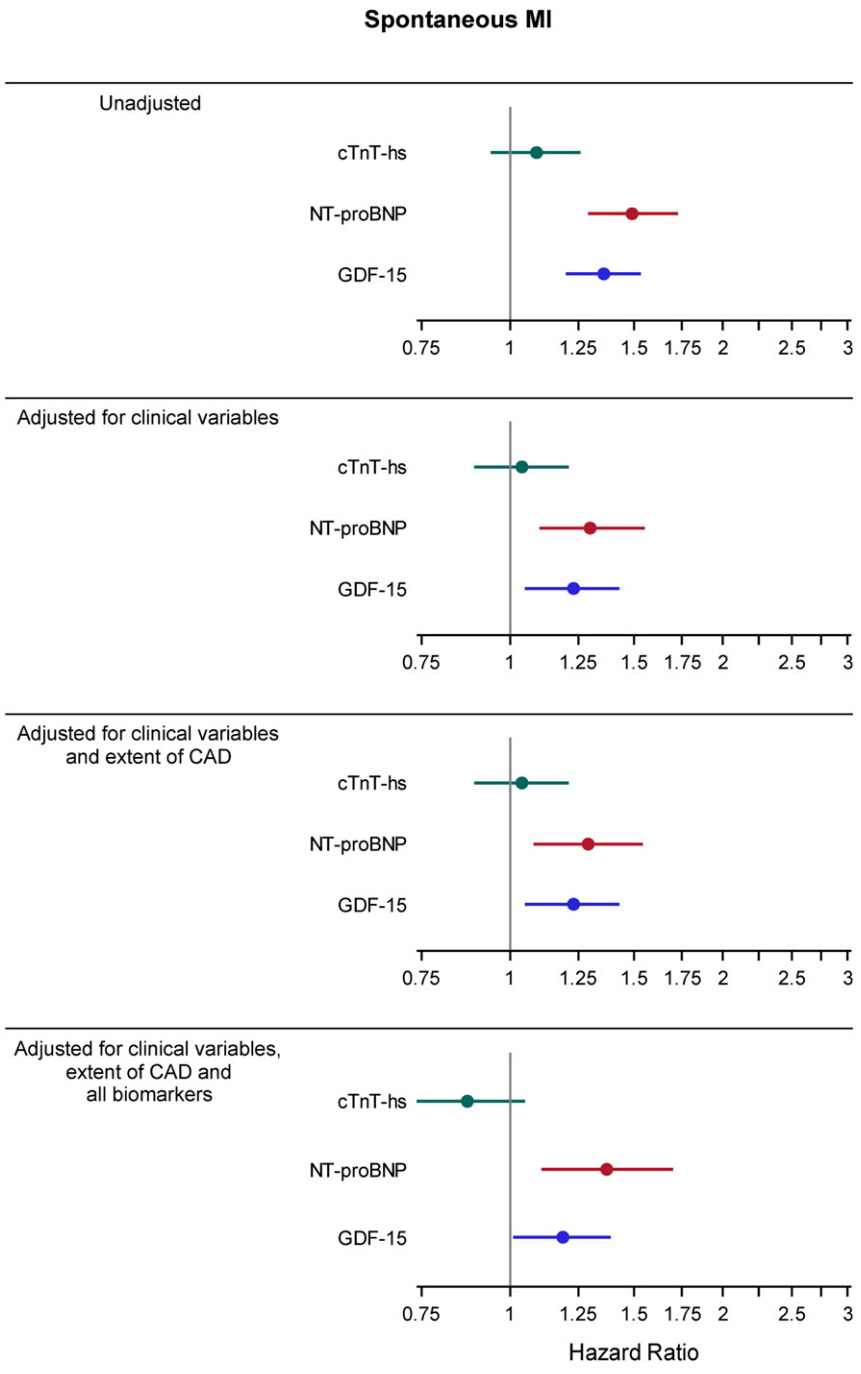
Figure 3



Prognostic value of natural log-transformed continuous biomarker addition to prediction models of cardiovascular death. Hazard ratio shown per SD of natural log-transformed continuous variable. The clinical variable model included the following variables: age, gender, diabetes mellitus, Killip class, admission heart rate, admission systolic blood pressure, history of congestive heart failure, peripheral arterial disease, cystatin C (log transformed), previous MI, previous PCI, previous CABG, and randomized treatment arm (ticagrelor/clopidogrel). Subsequently, the extent of CAD was added to the clinical variable model. The final model consisted of clinical variables, extent of CAD, and all log-transformed biomarkers (cTnT-hs, NT-proBNP, and GDF-15) simultaneously.

Figure 4



Prognostic value of natural log-transformed continuous biomarker addition to prediction models of spontaneous MI. Hazard ratio shown per SD of natural log-transformed continuous variable. See Figure 3 for model explanations.

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Appendix

Supplementary Table I. Baseline characteristics

	STEMI biomarker substudy (n = 5385)	Excluded STEMI patients (n = 759)
Age, median (IQR), y	59 (15)	60 (17)
Female sex, n (%)	1219 (22.6)	167 (22.0)
Risk factors, n (%)		
Habitual smoker	2526 (46.9)	377 (49.7)
Hypertension	3101 (57.6)	437 (57.6)
Dyslipidemia	2132 (39.6)	262 (34.5)
Diabetes mellitus	1023 (19.0)	158 (20.8)
History, n (%)		
MI	625 (11.6)	98 (12.9)
PCI	428 (7.9)	66 (8.7)
CABG	99 (1.8)	22 (2.9)
Congestive heart failure	112 (2.1)	10 (1.3)
Nonhemorrhagic stroke	129 (2.4)	29 (3.8)
Peripheral arterial disease	219 (4.1)	23 (3.0)
Chronic renal disease	150 (2.8)	20 (2.6)
Clinical findings		
Heart rate median (IQR), beat/min	75 (21)	75 (20)
Systolic blood pressure, median (IQR), mm Hg	131 (30)	130 (30)
Diastolic blood pressure, median (IQR), mm Hg	80 (20)	80 (17)
Killip class >2, n (%)	42 (0.8)	12 (1.6)
ECG findings at study entry, n (%)		
Persistent STE of 1 mm	5185 (96.3)	719 (94.7)
LBBB	321 (6.0)	59 (7.8)
Cystatin C at study entry, median (IQR), mg/L	0.75 (0.29), n = 5385	0.79 (0.26), n = 90
cTnT-hs at study entry, median (IQR), ng/L	147 (542), n = 5385	198 (446), n = 185
NT-proBNP at study entry, median (IQR), ng/L	221 (780), n = 5385	360 (926), n = 193
GDF-15 at study entry, median (IQR), ng/L	1492 (1004), n = 5385	1501 (979), n = 214

Abbreviations: *ECG*, Electrocardiogram; *STE*, ST elevation; *LBBB*, left bundle-branch block.

Supplementary Table II. Treatment characteristics and events during follow-up

	STEMI biomarker substudy (n = 5385)	Excluded STEMI patients (n = 759)
Delay from symptom onset to randomization, median (IQR), min	259 (348)	321 (479)
Delay from admission to randomization, median (IQR), min	42 (83)	57 (120)
Delay from first ECG to PCI, median (IQR), min	97 (131)	127 (245)
Delay from admission to PCI, median (IQR), min	76 (116)	102 (183)
Underwent primary PCI within 12 h of randomization, n (%)	4812 (89.4)	637 (83.9)
Location of coronary lesion, n (%)		
Left main	213 (4.0)	36 (4.7)
Left anterior descending	3626 (67.3)	512 (67.5)
Left circumflex	2158 (40.1)	321 (42.3)
Right	3213 (59.7)	430 (56.7)
Bypass graft	61 (1.1)	12 (1.6)
Extent of CAD, n (%)		
Zero/1-vessel disease*	2642 (49.1)	304 (42.9)
2-vessel disease	1623 (30.1)	214 (30.2)
3-vessel disease/left main	1120 (20.8)	190 (26.8)
Study drug, n (%)		
Ticagrelor	2682 (49.8)	371 (48.9)
Clopidogrel	2703 (50.2)	388 (51.1)
Study treatment duration, median (IQR), d	282 (180)	329 (180)
Antithrombotic treatment in hospital		
Aspirin	5310 (98.6)	728 (95.9)
Unfractioned heparin	3862 (71.7)	437 (57.6)
LMW heparin	2291 (42.5)	346 (45.6)
GP IIb/IIIa inhibitor	2287 (42.5)	323 (42.6)
Event during follow-up, n (%)		
Cardiovascular death	199 (3.7)	27 (3.6)
Myocardial infarction		
Procedure-related MI	68 (1.3)	12 (1.6)
Spontaneous MI	175 (3.2)	30 (4.0)
Cardiovascular death or spontaneous MI	345 (6.4)	51 (6.7)

Abbreviations: *LMW*, Low molecular weight; *GP*, glycoprotein.
*Nonsignificant CAD in 25 patients.

Supplementary Table III. Association between quartiles of biomarker levels and extent of CAD

	Biomarker Q1	Biomarker Q2	Biomarker Q3	Biomarker Q4	Cochran-Armitage trend test, *P* value
cTnT-hs, ng/L	n = 1344	n = 1349	n = 1347	n = 1345	
Median (min to max)	19 (2-41)	79 (41-147)	287 (148-583)	1357 (584-25747)	
Extent of CAD, n (%)					
Zero/1-vessel disease	663 (49.3)	664 (49.2)	655 (48.6)	660 (49.1)	.8216
2-vessel disease	407 (30.3)	402 (29.8)	425 (31.6)	389 (28.9)	.6775
3-vessel disease/left main	274 (20.4)	283 (21.0)	267 (19.8)	296 (22.0)	.4544
NT-proBNP, ng/L	n = 1348	n = 1346	n = 1345	n = 1346	
Median (min to max)	39 (3-70)	128 (71-221)	428 (222-850)	1877 (851-108979)	
Extent of CAD, n (%)					
Zero/1-vessel disease	778 (57.7)	671 (49.9)	595 (44.2)	598 (44.4)	<.0001
2-vessel disease	374 (27.7)	431 (32.0)	429 (31.9)	389 (28.9)	.5492
3-vessel disease/left main	196 (14.5)	244 (18.1)	321 (23.9)	359 (26.7)	<.0001
GDF-15, ng/L	n = 1346	n = 1346	n = 1347	n = 1346	
Median (min to max)	922 (345-1115)	1290 (1116-1492)	1730 (1492-2120)	2850 (2120-95419)	
Extent of CAD, n (%)					
Zero/1-vessel disease	735 (54.6)	702 (52.2)	633 (47.0)	572 (42.5)	<.0001
2-vessel disease	416 (30.9)	381 (28.3)	412 (30.6)	414 (30.8)	.7429
3-vessel disease/left main	195 (14.5)	263 (19.5)	302 (22.4)	360 (26.7)	<.0001

Q, quartile.

Supplementary Table IV. Interaction analyses of treatment effect (ticagrelor vs clopidogrel) according to quartiles of biomarkers

		Clopidogrel	Ticagrelor	HR (95% CI)	*P* value for interaction	Adjusted HR (95% CI)*	Adjusted *P* value for interaction
CVD							
	GDF-15 Q1	12/669 (1.8%)	6/677 (0.9%)	0.49 (0.18-1.31)	.2378	0.51 (0.19-1.37)	.2885
	GDF-15 Q2	10/681 (1.5%)	16/665 (2.4%)	1.67 (0.76-3.67)		1.65 (0.75-3.65)	
	GDF-15 Q3	17/688 (2.5%)	20/659 (3.0%)	1.23 (0.64-2.35)		1.24 (0.65-2.37)	
	GDF-15 Q4	61/665 (9.2%)	57/681 (8.4%)	0.92 (0.64-1.32)		0.96 (0.67-1.39)	
	NT-proBNP Q1	6/667 (0.9%)	10/681 (1.5%)	1.64 (0.60-4.52)	.4849	1.64 (0.60-4.51)	.5405
	NT-proBNP Q2	13/645 (2.0%)	11/701 (1.6%)	0.78 (0.35-1.75)		0.76 (0.34-1.71)	
	NT-proBNP Q3	20/707 (2.8%)	24/638 (3.8%)	1.34 (0.74-2.43)		1.35 (0.74-2.45)	
	NT-proBNP Q4	61/684 (8.9%)	54/662 (8.2%)	0.91 (0.63-1.32)		0.98 (0.68-1.42)	
	cTnT-hs Q1	8/671 (1.2%)	8/673 (1.2%)	1.00 (0.38-2.66)	.8134	1.06 (0.40-2.84)	.7064
	cTnT-hs Q2	16/662 (2.4%)	17/687 (2.5%)	1.03 (0.52-2.05)		1.05 (0.53-2.08)	
	cTnT-hs Q3	31/690 (4.5%)	24/657 (3.7%)	0.82 (0.48-1.39)		0.80 (0.47-1.36)	
	cTnT-hs Q4	45/680 (6.6%)	50/665 (7.5%)	1.14 (0.76-1.70)		1.20 (0.79-1.80)	
Spon MI							
	GDF-15 Q1	13/669 (1.9%)	10/677 (1.5%)	0.75 (0.33-1.72)	.2974	0.75 (0.33-1.71)	.3183
	GDF-15 Q2	23/681 (3.4%)	20/665 (3.0%)	0.91 (0.50-1.66)		0.86 (0.47-1.58)	
	GDF-15 Q3	23/688 (3.3%)	24/659 (3.6%)	1.09 (0.61-1.93)		1.08 (0.61-1.92)	
	GDF-15 Q4	40/665 (6.0%)	22/681 (3.2%)	0.53 (0.31-0.89)		0.53 (0.31-0.89)	
	NT-proBNP Q1	10/667 (1.5%)	8/681 (1.2%)	0.79 (0.31-2.00)	.3451	0.78 (0.31-1.97)	.4009
	NT-proBNP Q2	28/645 (4.3%)	15/701 (2.1%)	0.49 (0.26-0.92)		0.49 (0.26-0.91)	
	NT-proBNP Q3	28/707 (4.0%)	26/638 (4.1%)	1.04 (0.61-1.78)		0.98 (0.58-1.68)	
	NT-proBNP Q4	33/684 (4.8%)	27/662 (4.1%)	0.84 (0.50-1.40)		0.84 (0.50-1.40)	
	cTnT-hs Q1	23/671 (3.4%)	19/673 (2.8%)	0.82 (0.45-1.51)	.7009	0.83 (0.45-1.53)	.6615
	cTnT-hs Q2	25/662 (3.8%)	16/687 (2.3%)	0.62 (0.33-1.16)		0.60 (0.32-1.13)	
	cTnT-hs Q3	22/690 (3.2%)	21/657 (3.2%)	1.01 (0.56-1.84)		1.00 (0.55-1.82)	
	cTnT-hs Q4	29/680 (4.3%)	20/665 (3.0%)	0.70 (0.39-1.23)		0.67 (0.38-1.18)	

Abbreviations: *HR*, Hazard ratios with clopidogrel as reference; *CVD*, cardiovascular death; *spon MI*, spontaneous myocardial infarction.
*Adjusted for age, gender, diabetes mellitus, Killip class, admission heart rate, admission systolic blood pressure, history of congestive heart failure, peripheral arterial disease, cystatin C (log transformed), previous MI, previous PCI, and previous CABG.

Supplementary Table V. Multivariable Cox regression model cTnT-hs for outcome measures

Added biomarker cTnT-hs	No. of patients	CVD HR(95% CI)	Spon MI HR(95% CI)
Unadjusted: Q 1	1344		
Unadjusted: Q 2	1349	2.07 (1.16-3.87)	0.99 (0.64-1.52)
Unadjusted: Q 3	1347	3.49 (2.05-6.29)	1.05 (0.68-1.61)
Unadjusted: Q 4	1345	6.15 (3.73-10.85)	1.22 (0.81-1.85)
Unadjusted: Cont	5385	1.91 (1.66-2.22)	1.09 (0.94-1.26)
Model 1 + biom: Q 1	1344		
Model 1 + biom: Q 2	1349	1.75 (0.98-3.27)	0.95 (0.61-1.47)
Model 1 + biom: Q 3	1347	2.57 (1.50-4.65)	0.94 (0.61-1.46)
Model 1 + biom: Q 4	1345	3.67 (2.20-6.53)	1.07 (0.70-1.63)
Model 1 + biom: Cont	5385	1.61 (1.38-1.88)	1.04 (0.89-1.21)
Model 2 + biom: Q 1	1344		
Model 2 + biom: Q 2	1349	1.76 (0.98-3.29)	0.95 (0.61-1.46)
Model 2 + biom: Q 3	1347	2.61 (1.52-4.72)	0.95 (0.62-1.46)
Model 2 + biom: Q 4	1345	3.71 (2.22-6.60)	1.07 (0.70-1.65)
Model 2 + biom: Cont	5385	1.61 (1.38-1.87)	1.04 (0.89-1.21)
Model 3 + biom: Q 1	1344		
Model 3 + biom: Q 2	1349	1.67 (0.92-3.13)	0.84 (0.54-1.30)
Model 3 + biom: Q 3	1347	2.12 (1.20-3.95)	0.71 (0.45-1.13)
Model 3 + biom: Q 4	1345	2.53 (1.41-4.76)	0.73 (0.45-1.21)
Model 3 + biom: Cont	5385	1.32 (1.09-1.60)	0.87 (0.72-1.05)
Model 4 + biom: Q 1	1344		
Model 4 + biom: Q 2	1349	1.65 (0.92-3.11)	0.84 (0.54-1.31)
Model 4 + biom: Q 3	1347	2.20 (1.24-4.10)	0.74 (0.47-1.17)
Model 4 + biom: Q 4	1345	2.43 (1.35-4.61)	0.73 (0.45-1.20)
Model 4 + biom: Cont	5385	1.28 (1.07-1.55)	0.87 (0.72-1.05)
SD biom: 1.76			

Abbreviations: *Biom*, Biomarker; *Cont*, continuous. Continuous analysis HR: per SD of logarithm of biomarker. Quartile analysis: HRs represent ratios of each quartile compared to the first.
Model l: age, gender, diabetes mellitus, Killip class, admission heart rate, admission systolic blood pressure, history of congestive heart failure, peripheral arterial disease, cystatin C (log transformed), previous MI, previous PCI, previous CABG, randomized treatment arm (ticagrelor/clopidogrel).
Model 2: model 1 + extent of CAD.
Model 3: model 2 + NT proBNP.
Model 4: model 3 + GDF-15.

Supplementary Table VI. Multivariable Cox regression model NT-proBNP for outcome measures

Added biomarker NT-proBNP	No. of patients	CVD HR(95% CI)	Spon MI HR(95% CI)
Unadjusted: Q 1	1348		
Unadjusted: Q 2	1346	1.51 (0.81-2.89)	2.42 (1.42-4.30)
Unadjusted: Q 3	1345	2.80 (1.62-5.12)	3.11 (1.86-5.45)
Unadjusted: Q 4	1346	7.57 (4.63-13.27)	3.59 (2.17-6.26)
Unadjusted: Cont	5385	2.50 (2.16-2.90)	1.49 (1.29-1.73)
Model 1 + biom: Q 1	1348		
Model 1 + biom: Q 2	1346	1.21 (0.64-2.33)	2.10 (1.23-3.76)
Model 1 + biom: Q 3	1345	1.98 (1.13-3.65)	2.47 (1.46-4.39)
Model 1 + biom: Q 4	1346	3.46 (2.03-6.26)	2.48 (1.44-4.48)
Model 1 + biom: Cont	5385	1.75 (1.48-2.07)	1.30 (1.10-1.55)
Model 2 + biom: Q 1	1348		
Model 2 + biom: Q 2	1346	1.16 (0.62-2.23)	2.07 (1.21-3.70)
Model 2 + biom: Q 3	1345	1.81 (1.03-3.34)	2.39 (1.41-4.24)
Model 2 + biom: Q 4	1346	3.22 (1.89-5.84)	2.42 (1.40-4.37)
Model 2 + biom: Cont	5385	1.71 (1.45-2.03)	1.29 (1.08-1.54)
Model 3 + biom: Q 1	1348		
Model 3 + biom: Q 2	1346	0.99 (0.52-1.92)	2.21 (1.28-3.97)
Model 3 + biom: Q 3	1345	1.32 (0.73-2.51)	2.73 (1.56-4.98)
Model 3 + biom: Q 4	1346	1.98 (1.07-3.83)	2.93 (1.57-5.65)
Model 3 + biom: Cont	5385	1.43 (1.17-1.76)	1.41 (1.14-1.75)
Model 4 + biom: Q 1	1348		
Model 4 + biom: Q 2	1346	0.97 (0.51-1.88)	2.17 (1.26-3.90)
Model 4 + biom: Q 3	1345	1.29 (0.71-2.46)	2.66 (1.52-4.85)
Model 4 + biom: Q 4	1346	1.81 (0.98-3.53)	2.78 (1.48-5.37)
Model 4 + biom: Cont	5385	1.35 (1.10-1.66)	1.37 (1.11-1.70)
SD biom: 1.64			

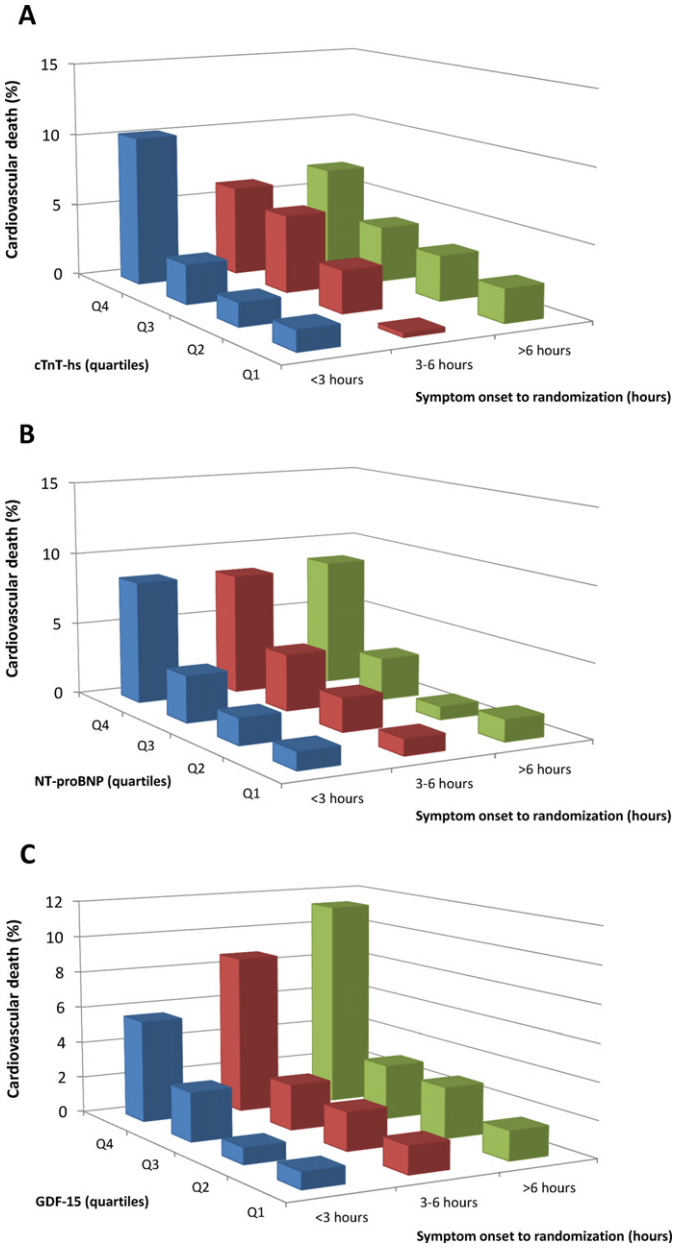
Abbreviations as in Table V.
Continuous analysis HR: per SD of logarithm of biomarker. Quartile analysis: HRs represent ratios of each quartile compared to the first.
Model l: age, gender, diabetes mellitus, Killip class, admission heart rate, admission systolic blood pressure, history of congestive heart failure, peripheral arterial disease, cystatin C (log transformed), previous MI, previous PCI, previous CABG, randomized treatment arm (ticagrelor/clopidogrel).
Model 2: model 1 + extent of CAD.
Model 3: model 2 + cTnT-hs.
Model 4: model 3 + GDF-15.

Supplementary Table VII. Multivariable Cox regression model GDF-15 for outcome measures

Added biomarker GDF-15	No. of patients	CVD HR(95% CI)	Spon MI HR(95% CI)
Unadjusted: Q 1	1346		
Unadjusted: Q 2	1346	1.46 (0.80-2.70)	1.90 (1.15-3.20)
Unadjusted: Q 3	1347	2.06 (1.19-3.71)	2.07 (1.27-3.46)
Unadjusted: Q 4	1346	6.91 (4.33-11.74)	2.90 (1.83-4.78)
Unadjusted: Cont	5385	1.82 (1.67-1.96)	1.36 (1.20-1.53)
Model 1 + biom: Q 1	1346		
Model 1 + biom: Q 2	1346	1.14 (0.63-2.13)	1.73 (1.05-2.94)
Model 1 + biom: Q 3	1347	1.27 (0.72-2.32)	1.69 (1.02-2.88)
Model 1 + biom: Q 4	1346	2.77 (1.64-4.94)	2.06 (1.22-3.58)
Model 1 + biom: Cont	5385	1.52 (1.34-1.70)	1.23 (1.05-1.43)
Model 2 + biom: Q 1	1346		
Model 2 + biom: Q 2	1346	1.11 (0.61-2.07)	1.72 (1.04-2.92)
Model 2 + biom: Q 3	1347	1.20 (0.68-2.19)	1.67 (1.00-2.84)
Model 2 + biom: Q 4	1346	2.63 (1.55-4.69)	2.03 (1.20-3.53)
Model 2 + biom: Cont	5385	1.52 (1.35-1.71)	1.23 (1.05-1.43)
Model 3 + biom: Q 1	1346		
Model 3 + biom: Q 2	1346	1.05 (0.58-1.96)	1.68 (1.01-2.84)
Model 3 + biom: Q 3	1347	1.10 (0.62-2.01)	1.60 (0.96-2.73)
Model 3 + biom: Q 4	1346	2.25 (1.32-4.04)	1.94 (1.14-3.38)
Model 3 + biom: Cont	5385	1.43 (1.26-1.62)	1.20 (1.01-1.40)
Model 4 + biom: Q 1	1346		
Model 4 + biom: Q 2	1346	1.07 (0.59-1.99)	1.66 (1.01-2.83)
Model 4 + biom: Q 3	1347	1.12 (0.63-2.04)	1.60 (0.96-2.73)
Model 4 + biom: Q 4	1346	2.27 (1.32-4.09)	1.91 (1.12-3.33)
Model 4 + biom: Cont	5385	1.42 (1.25-1.61)	1.19 (1.01-1.39)
SD biom: 0.54			

Abbreviations as in Table V.
Continuous analysis HR: per SD of logarithm of biomarker. Quartile analysis: HRs represent ratios of each quartile compared to the first.
Model l: age, gender, diabetes mellitus, Killip class, admission heart rate, admission systolic blood pressure, history of congestive heart failure, peripheral arterial disease, cystatin C (log transformed), previous MI, previous PCI, previous CABG, randomized treatment arm (ticagrelor/clopidogrel).
Model 2: model 1 + extent of CAD.
Model 3: model 2 + NT-proBNP.
Model 4: model 3 + cTnT-hs.

Supplementary Figure



Occurrence of CVD for quartiles of cTnT-hs (**A**), quartiles of NT-proBNP (**B**), and quartiles of GDF-15 (**C**) stratified according to time between onset of symptoms and randomization.